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DIURETIC THERAPY IN CARDIAC FAILURE*†

The abnormal physiology of congestive heart failure has been studied intensively for several centuries with gradual improvement in understanding and control. In the past ten years, remarkable advances have been made in therapy as a result of the discovery and development of unusually effective diuretic agents. Pharmacological studies of these drugs have not only bettered treatment, but have also clarified abnormal mechanisms involved in promoting and sustaining various edematous states. In the discussion that follows, certain aspects of the abnormal renal physiology of congestive heart failure will be reviewed briefly so that the actions of various diuretics may be put in proper perspective. A grasp of fundamental mechanisms is vital to thoughtful and resourceful therapy.

Renal Function in Heart Failure

The retention of salt and water with expansion of the extracellular fluid volume and the formation of edema may be traced to fundamentally appropriate but eventually excessive and persistent physiological adjustments by the kidneys. In normal man, the renal vasculature plays an important role in systemic circulatory reactions. Since one quarter or more of cardiac output perfuses the kidneys at rest and since the renal parenchyma is resistant to prolonged ischemia, intrarenal vasoconstriction may safely divert a considerable quantity of blood to more sensitive tissues, such as the heart or brain, when the need arises. During exercise, blood flow through active muscular tissue increases at the expense of the kidneys and by virtue of an increment in cardiac output. The added burden upon the heart is thus lessened by the extent to which renal blood flow is diminished.

Blood loss, traumatic shock and prolonged orthostasis are characterized by an inadequate circulating blood volume and by a fall in cardiac output that is offset to some extent by the renal vascular adjustment. In heart failure, also, whatever its etiology, the cardiac output is insufficient, either in relative (anemia, thyrotoxicosis) or in absolute (arteriosclerosis, hypertension) terms. The intrarenal vasoconstriction that develops may be regarded as a suitable response. With renal ischemia, however, even if no tissue damage occurs, urine formation is impaired by the fall in glomerular capillary pressure upon which filtration depends. Under most stressful conditions of relatively short duration, this deleterious side effect would have very little importance, but in heart failure the response persists indefinitely. It remains uncertain to what extent stimuli emanating from the heart itself, persistent release of neurohumoral agents or the tendency for the arterial pressure to fall may contribute in eliciting renal vasoconstriction. Cardiac output does tend to fall rather than rise during exertion in patients with heart failure, and arterial pressure is sustained only by intense vasoconstriction in which the kidney participates. Moreover, central venous pressure, already elevated, rises still more. Perhaps these circulatory factors set in train hormonal responses, such as release of vasopressin by the posterior pituitary, of aldosterone by the adrenal cortex, and of catecholamines by the adrenal medulla and autonomic nervous system. In any case, the renal circulatory reaction tends to persist, even at rest, and changes in renal tubular function develop that are difficult to ascribe to hypofiltration alone. All are conducive to water and salt retention; all are reversible on correction of the cardiac fault.

Glomerular filtration is the chief determinant of tubular function in providing the critical loading mixture of substrate for processing, the vehicle for transportation of secreta and most of the energy for the movement of excreted materials from blood to the renal pelvis. Neverthe-

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less, the tubular cells are not to be regarded as mechanically responsive to the character and quantity of filtrate conveyed to them. It is true that even a minor reduction in filtration may diminish the urinary output of electrolytes and water in the face of excess intake and body content, but tubular adjustments can be made within wide limits, and balance can often be restored without detectable alteration in glomerular function. For the most part, tubular reabsorption and secretion depend upon active transport processes in which movement of solute against a concentration gradient is facilitated by intracellular carrier systems, by the generation of electropotential differences, by ionic exchange and by many other mechanisms as yet poorly understood or unsuspected. The use of the micropuncture technique by Walker, Bott, Gottschalk and others to obtain samples of fluid from different parts of the renal tubules has made it possible to demonstrate that sodium and chloride are rapidly removed from glomerular filtrate as it passes down the proximal convoluted tubule. Since the fluid remains in osmotic equilibrium with the plasma, and since studies of sodium excretion during intense osmotic diuresis indicate that more than 80 per cent of the filtered sodium is reabsorbed when more than 50 per cent of the glomerular filtrate enters the urine, it is widely believed that proximal tubular reabsorption of sodium is primary and that chloride and water follow sodium passively in the maintenance of isosmoticity.

Sodium appears to be taken up in the distal convoluted tubule, partly by exchange for hydrogen and potassium ions. The former are apparently derived, for the most part, from carbonic acid generated from carbon dioxide by hydration under the influence of the enzyme, carbonic anhydrase. Recent work suggests that hydrogen-sodium exchange may be operative similarly in the proximal tubule. This system promotes bicarbonate reabsorption by acidifying the tubular fluid with the formation of carbonic acid from sodium bicarbonate and subsequent release of carbon dioxide which readily diffuses out of the tubule. Part of the sodium ion conserved by the distal tubule also is replaced, in effect, by ammonium ion which is generated by the combination of hydrogen ion with ammonia formed and secreted by distal tubular cells.

In addition to these mechanisms, the ascending limb of the loop of Henle and the distal tubule, including the collecting duct, appear to be capable of abstracting sodium chloride from the tubular urine with the production of hypotonic urine. (The water in excess of that required for isosmoticity in dilute urine is referred to as "free water," i.e., a theoretical volume of water freed of solute.) The brilliant work of Wirz, Berliner, Gottschalk and others has recently done much to clarify the mechanisms of urinary concentration. Their evidence indicates that selective transfer of sodium chloride from urine into the interstitium by the hairpin loops of Henle and sluggish "washout" of solute as a result of the parallel looped (counter-current) arrangement of the capillaries creates in the medullary papillae a persistently hypertonic milieu. The osmotic extraction of water from the small residual volume of filtrate passing down the semipermeable (under control of vasopressin) collecting tubules through the medulla would then account satisfactorily for the hypertonicity of the urine.

From the information now available, none of these mechanisms seems to be impaired by the circulatory defects of heart failure. Following correction of failure, no abnormality is evident and, with the exception of congestion and necrotizing tubular lesions produced by profound ischemia in terminal failure, no tubular damage occurs. The evidence suggests, in fact, that the tubules are functioning normally, but inappropriately with respect to control of body fluid volume. Diuretic agents are used in heart failure to interfere with tubular conservation of electrolytes (especially sodium) and to produce specific renal dysfunctions designed to restore extracellular fluid volume to normal.

Diuretic Agents

Each of the four categories of diuretics having major therapeutic significance interferes with one or more of the tubular transfer systems for sodium. These are: (1) the organic mercurial diuretic compounds (proximal sodium reabsorption); (2) the chloruretic sulfonamides of which chlorothiazide is the prototype (both proximal and distal sodium uptake); (3) the sulfonamides inhibiting carbonic anhydrase (hydrogen-sodium exchange); and (4) the 17-spirolactone steroid type of aldosterone inhibitors. The use of these four varieties, which have entirely different pharmacological actions, alone or in combination, has not only greatly enhanced the control of cardiac edema but has also contributed to the elucidation of renal tubular function.

Mercurial Diuretics. The organic mercurial diuretics have long been and remain among the most important therapeutic agents available to the physician. Discovered some 40 years ago in the search for antisyphilitic agents, they have been extensively employed and studied. The forms in common use today are mercuripropyl compounds in which mercury is usually linked ionically with theophylline to increase solubility and to reduce local irritation at the site of intramuscular injection. Govaerts was the first to prove, in a classic experiment, that these drugs act directly upon the kidney. Since then, numerous studies have shown that they are fixed in the renal cortex, ultimately excreted in the urine, and in excess dosage may damage the proximal con-

voluted tubule. Much additional evidence supports the view that the mercurial diuretics interfere with proximal sodium reabsorption, but the dependence of diuresis upon the presence of chloride and the preponderance of chloride in the urine has been interpreted as evidence of primary interference with chloride reabsorption. Recent studies by Mudge and Weiner suggest that hyperchloremic acidosis may potentiate mercurial diuresis by reducing pH within tubular cells and thus facilitate liberation of divalent mercuric ions to block renal enzyme. Kessler, Lozano and Pitts believe that steric configuration of the mercurial may have greater importance in determining diuretic activity. In any case, the diuresis is relatively hypotonic, presumably because distal tubular mechanisms are unaffected and free water can be generated. These agents may therefore be useful in hyponatremic states in which water has been retained in excess of sodium. Mercurial diuretics can be given in full dosage intramuscularly on an almost daily basis in most instances. When used too frequently, however, the diuretic effectiveness is lessened and occasionally hypokalemic, hypochloremic alkalosis develops. Organic chlorides, such as *l*-arginine and *l*-lysine monohydrochloride, have been introduced recently as substitutes for ammonium chloride in the correction of this condition because they are less upsetting. Much larger doses are needed, however, in order to administer the same amount of chloride. Potassium depletion is much less common with mercurial diuretics than with chlorothiazide derivatives, possibly because mercurial compounds also act to suppress tubular secretion of potassium.

Chlorothiazide and its Derivatives. Chlorothiazide, a heterocyclic sulfonamyl derivative, has proved to be an unusually effective agent of great value clinically because it can be given by mouth. In vitro, it inhibits carbonic anhydrase, a property which led to its discovery, but in vivo it produces less change in bicarbonate excretion than expected. Indeed, anion reabsorption is interfered with unselectively so that chloruresis is not predominant, and diuresis is not potentiated by chloride or by any other anion. Chlorothiazide seems to act primarily upon proximal sodium reabsorption. The excessive potassium loss so often associated with its use may be merely the consequence of diversion of more sodium to the distal tubular site to exchange for potassium. Free water clearance is not increased when chlorothiazide is given intravenously during maintained water diuresis, as it is when mercurial diuretics are administered under the same conditions. This finding suggests that chlorothiazide acts in the distal tubule to inhibit sodium reabsorption at the site of free water formation. The effectiveness of chlorothiazide, when used alone or in combination with mercurial agents, in patients resistant to the mercurial diuretic alone may be thus explained.

Chlorothiazide and its derivatives possess a number of other interesting but poorly understood pharmacological activities. This group of compounds may produce urate retention and hyperuricemia, although episodes of acute gout are but rarely precipitated. Glomerular filtration usually falls 15 to 20 per cent with a corresponding rise in blood urea nitrogen concentration, possibly accounting for the reduction in urine flow in patients with diabetes insipidus that other diuretics do not produce. In addition, hyperglycemia can be produced in certain patients with diabetes mellitus. These actions of chlorothiazide do not ordinarily constitute a contraindication to its usage.

Chlorothiazide is remarkably well tolerated, and toxic manifestations have been rare. However, unlike mercurial agents, instances of blood dyscrasias, jaundice, and acute pancreatitis have been reported. Many derivatives of chlorothiazide have been developed, but these agents also cause potassium depletion and no pharmacological advantage has been established for the derivatives, except possibly in the case of chlorthalidone, a compound with a phthalamidine grouping which may have an unusually prolonged action—up to 72 hours after a single dose according to one report.

Carbonic Anhydrase Inhibitors. Acetazolamide (Diamox) is the best known of the sulfonamides which inhibit carbonic anhydrase. These compounds differ from chlorothiazide and its derivatives in producing a very large increase in bicarbonate excretion without chloruresis. The enzyme inhibition is transient so that refractoriness usually develops in about 48 hours, and these compounds should be used intermittently. Carbonic anhydrase inhibitors often produce potassium deficiency and hyperchloremia. The latter may be useful in preparing patients for a mercurial diuresis, but for unexplained reasons the carbonic anhydrase inhibitor must be stopped before the mercurial injection because, when given with a mercurial agent, diuresis is reduced. In contrast, acetazolamide administration potentiates the diuresis of chlorothiazide.

While this group of compounds remains of considerable theoretical and historical interest, from a practical point of view their use in therapy is rarely necessary. Occasionally, acetazolamide, 250 mg., once to three times daily, may be useful in preparing patients for mercurial diuresis or in augmenting a chlorothiazide regimen. The compound may still have a special place in the treatment of heart failure associated with pulmonary disease and chronic CO_2 retention, but here the benefits may be due, not only to the diuretic action, but also to stimulation of

the respiratory center, possibly as a result of an accentuation of the metabolic acidosis.

Aldosterone Inhibitors. A group of compounds of great importance theoretically as well as practically (the steroidal 17-spirolactones) has recently been developed. These compounds appear to interfere specifically with the action of aldosterone upon the renal tubule; they are inert in adrenalectomized animals, but act to block the sodium-retaining and kaliuretic action of either administered or endogenous aldosterone. One, 3 (3-keto-7α acetylthio-17β hydroxy-4-androsten-17γ-yl) — propionic acid γ — lactone, is now available commercially as Aldactone and can be administered in dosages of from 200 to 1,200 mg. per day, orally. Aldactone appears to be well tolerated and is virtually free of serious toxicity.

Quantitatively, the spirolactones are slower to act and are not nearly as potent as either mercurial agents or chlorothiazide in promoting sodium and water excretion. However, qualitatively, these agents are unique amongst known diuretics in that they do not cause increased potassium excretion. They may be most useful in combination with chlorothiazide and its derivatives because they can block the potassium loss so often produced by chlorothiazide. Owing to their different mode of action, spirolactones may be useful in patients resistant to other diuretic agents, either alone or as a means of potentiating the action of chlorothiazide or mercurial diuretics. Spirolactones are most effective in cirrhosis of the liver with ascites where large excesses of aldosterone are produced. In congestive heart failure, the results may be disappointing, perhaps because hemodynamic factors are more important in sustaining sodium retention.

Approach to Treatment

The proper management of the patient with congestive heart failure depends upon careful appraisal of physiological disturbances and application of suitable pharmacological measures. For simple, uncomplicated clinical problems, any one of the agents discussed above can be used successfully. However, since these compounds may have very different effects on electrolyte metabolism, it is more important than ever before to obtain also a base line evaluation of the renal status and electrolyte balance. Unfortunately, hypokalemia, hyponatremia, alkalosis or mild azotemia may be present without symptoms. An adequate response to diuretic therapy depends not only upon a studied effort to correct the cardiac dysfunction but also upon the establishment of the most favorable circumstances for an increase in water and salt excretion. Hyponatremia, hypokalemia, hypochloremia, alkalosis and anemia all interfere with the diuretic response. Even commonplace and "normal" physiological responses may have a detrimental influence. Thus, the intrarenal vasoconstriction of the upright position, exertion, anxiety and fatigue are grossly exaggerated in the patient with failure and must be guarded against. Serous effusions and gravitational shifts of fluid to the lower parts of the body may effectively sequester large quantities of extracellular fluid that can be removed directly or mobilized by appropriate manipulations. Diuretics should never be used without due regard for the total situation.

Chlorothiazide, or one of its derivatives, is the diuretic agent of choice because of its rapidity of action, potency and ease of administration. Because potassium depletion is so readily produced, and may at times develop after only three or four days of administration, chlorothiazide should not be given in full dosage (2 Gm. per day), except on an intermittent basis. Maximal diuresis may not appear until the second day. Accordingly, a program of three or four consecutive days of treatment, followed by a two- to four-day interval without treatment, seems reasonable. It has been demonstrated that 250 mg., given every three hours, produce a greater diuresis than 500 mg., every six hours, in patients with heart failure. One or two 250 mg. tablets, given at three-hour intervals beginning in early morning, appear to be a minimal initial dosage. The amount may then be doubled and the dosage schedule increased to four times a day, if necessary. The use of potassium supplements 3 to 6 Gm. KCl daily) may also be necessary, but this therapy in itself can be hazardous in sodium-depleted subjects, and an increased fruit intake may obviate the need for potassium supplements.

One should remember that a serious cardiac arrhythmia can develop in potassium-depleted patients who are receiving digitalis. Mercurial diuretic agents not only augment the natruresis, but may also block the kaliuresis of chlorothiazide. However, this combination is probably not suitable for long-term management, and in patients where potassium depletion is a special problem, chlorothiazide should be combined with spirolactone. The hazards of potassium depletion are lessened by a moderate or a liberal sodium intake, and it has been shown that the most severely sodium-depleted patients with avid renal sodium retention are most prone to potassium depletion when receiving chlorothiazide.

The newer derivatives of chlorothiazide, although more powerful quantitatively, have not been clearly shown to be more potent than chlorothiazide itself when full dosages are compared. Occasionally, however, patients have seemed to respond better to one of the new derivatives. These compounds have been developed faster than they can be properly evaluated. They may, in fact, offer many advantages, but until more precise information is available, they should be employed

with caution and always with skepticism for the claims of their superiority.

In the most resistant instances of congestive heart failure, chlorothiazide may be combined, not only with mercurial agents and with spirolactones, but also with adrenal steroid-type compounds, such as prednisone. Possibly these glucocorticoids, as well as the theophylline compounds, aid diuresis by increasing glomerular filtration. Another potent regimen involves the production of hyperchloremic acidosis with the use of ammonium chloride and/or acetazolamide for several days prior to the injection of a mercurial diuretic. In the presence of hyperchloremic acidosis, a mercurial agent may produce a satisfactory diuresis after other measures have failed.

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